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ASSOCIATE VICE PRESIDENT
US REGULATORY AFFAIRS



8347107 August 7, 2001-7 P3:15

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 00N-0074; Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products; Interim Rule; 66 Federal Register 20589-20600, April 24, 2001

Dear Sir/Madam:

The following comments on the above interim rule are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives; our members are investing over \$30 billion in 2001 for the discovery and development of new medicines.

PhRMA welcomes FDA's Interim Rule to enhance the protections for children and adolescents included in clinical research and agree that, for the reasons identified by FDA in the Background to the Interim Rule, the number of studies being conducted in pediatric groups has multiplied several fold in recent years. Moreover, it is clear that public and professional concern with many aspects of the federal regulation of clinical research is resulting in important changes to the structure and practice of federal oversight¹. Subpart D of the "Federal Common Rule"² has provided important and necessary additional protections to members of pediatric groups enrolled in federally-funded studies since 1983, and these protections have been endorsed by the authoritative professional group³. It is, therefore, entirely appropriate that FDA should extend the same protections to pediatric populations included in clinical studies performed under its jurisdiction. However, by virtue of the fact that the language of Subpart D is now nearly 20 years old, and that much has been learned about the practicalities of protecting research participants during that time, PhRMA believes that FDA should modernize certain of its provisions in order to create an environment for pediatric research that is consistent with the expectations of researchers and patients and their families in the 21st century.

In §50.3(r) of the Interim Rule, FDA defines "permission" as "[t]he agreement of parent(s) or guardian to the participation of their child or ward in a clinical investigation." PhRMA agrees that this definition is appropriate, and that it is necessary to have this term to distinguish children from other research participants.

¹ There are many examples of these changes, but perhaps the two most significant have been the relocation of the former Office of Protection from Research Risks (OPRR) from the National Institutes of Health to become the Office of Human Research Protections (OHRP) at the Department of Health and Human Services, and the recent creation of the Office of Human Research Trials (OHRT) within FDA.

² 45 CFR 46, Subpart D.

³ See "Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations", Policy No. RE9503 of the American Academy of Pediatrics (*Pediatrics* (1995) Vol. 95, pp. 286-294).

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In §50.3(s) of the Interim Rule, FDA defines "guardian" as "[a]n individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care when general medical care includes participation in research. For purposes of subpart D of this part, a guardian also means an individual who is authorized to consent on behalf of a child to participate in research." This definition appears to leave open the possibility, admittedly an improbable one, that a guardian could be a person who is authorized to consent to a child's participation in research, but not authorized to consent to general medical care. PhRMA believes that this would be wholly undesirable for the child, and that the language should be clarified to require that no one may consent to a child's participation in research who is not also authorized to consent to the child's general medical care. Further, it would appear that many State laws do not specifically authorize a guardian to permit a child's involvement in research, so the present definition may be very restrictive in practice. PhRMA believes that adequate protection for children would result from the requirement that guardians should be authorized to consent to general medical care and that they should be *in loco parentis*, that is, with a legally enforceable duty to care for the totality of the child's interests.

In §50.52 of the Interim Rule, FDA codifies the circumstances in which an IRB may approve research in children involving greater than minimal risk but presenting the prospect of direct benefit to individual participants. In relation to this, FDA solicits comment on appropriate criteria for IRBs to use in assessing when a clinical investigation may involve more than minimal risk to children. PhRMA believes that the critical factors in this assessment will be:

- ◆ the age and degree of physiological maturity of the child;
- ◆ the nature and natural history of the clinical condition to be treated;
- ◆ the presence of complicating clinical conditions;
- ◆ the efficacy and safety of the treatment that may have been demonstrated in older patients, or that is expected on the basis of other clinical or preclinical investigations;
- ◆ the likely duration of treatment, and its impact upon the growth and development of the child.

A formulation of criteria for the assessment of more than minimal risk must be based upon an appropriate definition of minimal risk. PhRMA suggests that the definition of minimal risk should be in terms of the nature and intensity of the short and long term effects of the treatment, based upon consideration of the factors above. Thus, a minimal risk would be associated with a treatment that caused no more than short term risk or distress (1-2 days) of no more than moderate intensity (assessed by appropriate physiological and behavioral indicators), and which would be known or strongly expected not to have any unwanted consequences for the child's growth, development or welfare over the long term (months-years). PhRMA suggests that this definition is appropriate because it reflects the normal experience of childhood. This definition provides a basis upon which to assess greater than minimal risks, but PhRMA suggests that the balance of the assessment must always be towards the long term consequences of the treatment, rather than the short-term consequences, many of which are likely to be medically manageable. As FDA has stated in the Background to the Interim Rule, difficulties may often arise when the clinical circumstances change during a study. Investigations that were approved originally on the basis of a favorable balance of risks and benefits may, quite suddenly, present risks that are significantly greater. PhRMA believes that the conceptual basis for the consideration of risks that we have proposed will be just as applicable in these situations, in order to decide whether a particular participant should be withdrawn from a study, or whether an amendment to the study protocol is necessary.

FDA also recognizes that the requirement in §50.52 for the prospect of direct benefit to individual subjects may create ambiguities over the use of placebo controls in children, and invites comment on this issue. PhRMA supports the views of the American Academy of Pediatrics on this point⁴, and particularly that placebo controls may only be used ethically in children if their use does not place children at increased risk. "Risk" is defined to include not only risk of mortality or increased or irreversible morbidity, but also physical pain or other distress, including fear and inconvenience. PhRMA recommends that these points should be codified in the Rule.

In §50.53 of the Interim Rule, FDA proposes conditions under which an institutional review board (IRB) may approve research involving greater than minimal risk, but with no prospect of direct benefit to the study participants, and requests commentary upon whether further definition should be provided to aid IRBs in making graduated determinations of risk. PhRMA believes that further guidance would be helpful, but is probably difficult to give in other than very general terms, as the variables to be considered will be so numerous and specific to each study situation. It would be important that flexibility to protect children should not be lost.

PhRMA agrees with FDA that wards need special protections, and appreciates that much has been done to prevent abuses of children in institutions by the provisions of §50.56 of the Interim Rule. PhRMA notes that FDA is soliciting comments on the practicalities of appointing advocates for wards, and encourages FDA to persist with this concept, although we believe that the requirement to appoint advocates will often add markedly to the complexity of conducting studies in institutionalized children. FDA should clarify in the Interim Rule, or in a guidance document, the following aspects of the appointment of advocates:

- ◆ How is the appointment of an advocate to be made? What are the obligations and responsibilities of advocates? How is the appointment of an advocate to be documented? What is a sponsor's role, and what are his responsibilities, in monitoring the appointment of advocates?
- ◆ When a study is approved by a central IRB, and one or more of the study sites wishes to enroll wards, must the central IRB take responsibility for the appointment of advocates, in spite of the fact that this may be administratively complex for it, and that it may not have much local knowledge of the study site or the wards or their circumstances? If not, what alternative provisions are optimal?
- ◆ When patients must be entered into a study acutely, by virtue of their medical condition, the appointment of an advocate before enrollment of a patient may be impractical. Does this mean that wards may not be included in this type of study?

In their analysis of the economic impacts of the implementation of the Interim Rule, FDA states that it has assumed that there will be no costs to sponsors associated with clinical holds. While PhRMA believes that FDA's reasons for making this statement are plausible and note that FDA has not calculated the potential impact of widespread accreditation of IRBs, that is likely to commence in the US over the next 1-2 years. PhRMA expects that inspections of studies in progress will be common as IRBs go through the accreditation process. Further, some IRBs may choose to inspect some studies more often than is strictly necessary under regulations, in order to avoid findings of non-compliance (by either IRBs or investigators) by accrediting bodies. Of all studies, PhRMA believes that pediatric studies would be amongst those most likely to attract additional inspections by IRBs, because of the sensitivity of the associated issues.

⁴ See footnote 3.

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Additional inspections by IRBs will probably discover more often (than if these inspections were not occurring) circumstances in which studies will be put on clinical hold. Therefore, PhRMA does not agree that FDA is necessarily justified in reckoning that no costs associated with clinical holds will result from implementation of the Interim Rule. PhRMA recommends that FDA should explicitly consider these possibilities in the Final Rule.

Sincerely,

A handwritten signature in cursive script, reading "Alan Goldhamer". The signature is written in dark ink and is positioned below the word "Sincerely,".